PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR PENTAZOCIN LACTATE INJECTION BP 30 mg/ml

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1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted Daily Exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects. In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of **Pentazocine Lactate Injection BP 0.05 mg/ml** for Injection have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

2. INTRODUCTION:

Pentazocine is a painkiller used to treat moderate to severe pain. It is believed to work by activating (agonizing) κ-opioid receptors (KOR) and μ-opioid receptors (MOR). As such it is called an opioid as it delivers its effects on pain by interacting with the opioid receptors. It shares many of the side effects of other opioids like constipation, nausea, itching, drowsiness and respiratory depression, but unlike most other opioids it fairly frequently causes hallucinations, nightmares and delusions.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

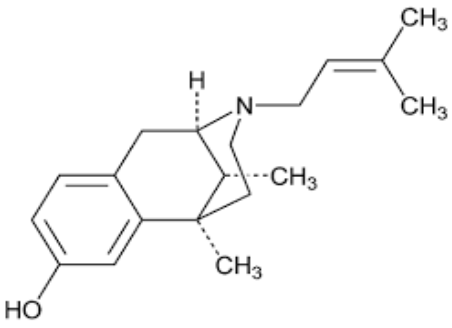
Pentazocine is a white or light yellowish-white odorless crystalline powder. Pentazocine is insoluble in water, but somewhat soluble in ethanol and soluble in acetic acid and chloroform. The melting point of Pentazocine has a range of 302 - 316°F (150°C - 158°C).

IUPAC Name: 2-dimethylallyl-5,9-dimethyl-2'-hydroxybenzomorphan.

Chemical Formula: $C_{19}H_{27}NO$

Molecular Weight: 285.42 g/mol

Molecular Structure:



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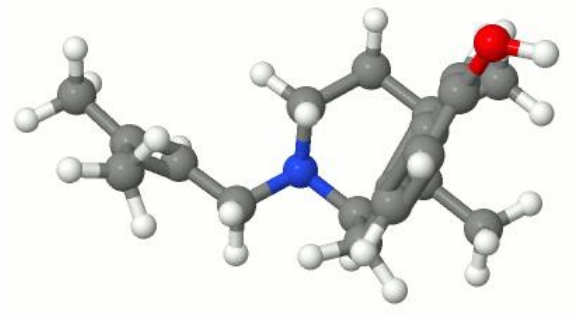

3D

4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
Toxicity	**Yes**	**No**	**Unknown**
Genotoxicant	-	-	√
Carcinogen	-	-	√
Reproductive/Developmentaltoxicity	-	-	√
Highly sensitizingpotential	-	-	√

5. SUMMARY OF ASSESSMENT PROCESS:

HAZARD IDENTIFICATION	
Pharmacodynamics data	Pentazocine is a potent analgesic which when administered orally in a 50 mg dose appears equivalent in analgesic effect to 60 mg (1 grain) of codeine. Onset of significant analgesia usually occurs between 15 and 30 minutes after oral administration, and duration of action is usually three hours or longer. Onset and duration of action and the degree of pain relief are related both to dose and the severity of pretreatment pain. Pentazocine weakly antagonizes the analgesic effects of morphine and meperidine; in addition, it produces incomplete reversal of cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. Pentazocine has about 1/50 the antagonistic activity of nalorphine. It also has sedative activity.
Pharmacokinetic data	**Absorption:** Pentazocine is well absorbed after intramuscular or subcutaneous administration and is extensively metabolized in the liver. **Metabolism:** The metabolites are excreted by the kidney with only a small amount of unchanged drug excreted in the urine. Peak plasma concentrations occur 15 minutes to 1 hour after intramuscular administration and the elimination half-life in plasma ranges between 2 and 5 hours.
Acute toxicity	Acute toxicity studies were carried out in mice and rats. Oral median lethal dose in rat and mice is 430 mg/kg.
Repeated dose toxicity	Data related to the repeated dose toxicity studies of Pentazocine is not available in the literature.
Carcinogenicity	Long term animal studies to evaluate the carcinogenic potential of Pentazocine have not been conducted.
Genotoxicity studies	Studies to evaluate the mutagenic potential of Pentazocine have not been conducted.
Reproductive/Developmental Toxicity	Animal studies to evaluate the reproductive and developmental toxicity of Pentazocine have not been conducted.

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HAZARD IDENTIFICATION	
Highly sensitizing potential	Data related to sensitizing potential of Pentazocine lactate is not available in literature.
Hazard Identification Symbol	 Acute Toxicity
IDENTIFICATION OF CRITICAL EFFECTS	
Clinical therapeutic and Adverse effects	Pentazocine lactate is indicated for postoperative pain, chronic pain, as an effective analgesic during labour, in myocardial infarction and in acute pain of renal or biliary colic. Adverse effects include nausea, dizziness or lightheadedness, vomiting, euphoria, respiratory depression, dyspnea, shock, hypertension, insomnia, disorientation, dry mouth, constipation, blurred vision, muscle tremor.

NOAEL/LOAEL/NOEL/LOEL	Human therapeutic dose of 30 mg is selected for PDE calculation.

APPLICATION OF ADJUSTMENT FACTORS- PDE calculation		
F1: Extrapolation between species	1	Human therapeutic dose is selected.
F2: Inter-individual variability	10	Conventionally used to allow for differences betweenindividuals in the human population
F3: Duration of toxicity	1	Human therapeutic dose is selected.
F4: Severe toxicity (1-10)	10	For observed adverse effects and boxed warning in humans.
F5: NOAEL Vs LOAEL (10 if LOAEL)	10	Human therapeutic dose is selected and considered as LOAEL.

PDE CALCULATION:

$$\text{PDE (mg/day)} = \frac{\text{Human Therapeutic Dose}}{\text{F1x F2 x F3 x F4 x F5}}$$

$$= \frac{30}{1 \times 10 \times 1 \times 10 \times 10}$$

= **0.03 mg/day**

6. REFERENCES:

- https://go.drugbank.com/drugs/DB00652
- https://pdf.hres.ca/dpd_pm/00044868.PDF
- https://pubchem.ncbi.nlm.nih.gov/compound/Pentazocine-lactate
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/016194s079s080lbl.pdf
- https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-setting-healthbased-exposure-limits-use-risk-identification-manufacture-different_en.pdf.
- https://cdn.pfizer.com/pfizercom/products/material_safety_data/TALWIN(Pentazocine)Injection_(Hospira)_9-Aug-2016.pdf

7. GLOSSARY:

PDE: Permitted daily exposure
AUC: Area under the curve
GRAS: Generally regarded as safe
GLP: Good laboratory practice
GMP: Good manufacturing practice
LD: Lethal dose
LED: Lowest-effective dose
TDLo (Toxic Dose Low): Lowest published toxic dose
LOAEL: Lowest-observed-adverse-effect level
LOEL: Lowest-observed-effect level
MSDS: Material safety data sheet
MTD: Maximum tolerable dose
MPDD: Maximum permissible daily dose
MTEL: Maximum tolerable exposure level**NEL:**
No-effect level
NOAEL: No-observed-adverse-effect level
NOEL: No-observed-effect level
OEL: Occupational exposure limit
QSAR: Quantitative structure–activity relationship
SDS: Safety data sheet
ADI: Acceptable daily intake. Estimate by JECFA; the amount of a food additive, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk.

Area under the curve (AUC): Area between a curve and the abscissa (horizontal axis), i.e., the area underneath the graph of a function; often, the area under the tissue (plasma) concentration

curve of a substance expressed as a function of time.

Bioaccumulation: progressive increase in the amount of a substance in an organism or partof an organism that occurs because the rate of intake exceeds the organism's ability to remove the substance from the body.

Bioavailability: biological and physiological availability. Extent of absorption of a substanceby a living organism compared to a standard system.

Biological half-life: for a substance, the time required for the amount of that substance in a biological system to be reduced to one-half of its value by biological processes, when the rate of removal is approximately exponential.

Carcinogen: agent (chemical, physical, or biological) that is capable of increasing the incidence of malignant neoplasms, thus causing cancer.

Clastogen: agent causing chromosome breakage and (or) consequent gain, loss, or rearrangement of pieces of chromosomes.

Clearance: volume of blood or plasma or mass of an organ effectively cleared of a substance by elimination (metabolism and excretion) divided by time of elimination.

Cmax: used in pharmacokinetics referring to the maximum (or peak) serum concentrationthat a drug achieves in a specified compartment or test area after the drug has been administrated and before the administration of a second dose.

Critical dose: dose of a substance at and above which adverse functional changes, reversible or irreversible, occur in a cell or an organ.

Critical effect: for deterministic effects, the first adverse effect that appears when the threshold (critical) concentration or dose is reached in the critical organ:

Adverse effects with no defined threshold concentration are regarded as critical. Dose (of a substance): total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue.

Draize test: evaluation of materials for their potential to cause dermal or ocular irritation and corrosion following local exposure; generally using the rabbit model (almost exclusively the New Zealand White) although other animal species have been used.

Elimination (in toxicology): disappearance of a substance from an organism or a partthereof, by processes of metabolism, secretion, or excretion.

Embryotoxicity: production by a substance of toxic effects in progeny in the first period of pregnancy between conception and the fetal stage.

Fetotoxicity: production by a substance of toxic effects in progeny in the second period of pregnancy between fetal stage and delivery.

First-pass effect: biotransformation and, in some cases, elimination of a substance in theliver

after absorption from the intestine and before it reaches the systemic circulation.

Gavage: administration of materials directly into the stomach by esophageal intubation.

Generally regarded as safe (GRAS): phrase used to describe the USFDA philosophy that justifies approval of food additives that may not meet the usual test criteria for safety but have been used extensively and have not demonstrated that they cause any harm to consumers.

Genotoxic: capable of causing a change to the structure of the genome.

Good laboratory practice (GLP) principles: fundamental rules incorporated in OECD guidelines and national regulations concerned with the process of effective organization and the conditions under which laboratory studies are properly planned, performed, monitored, recorded, and reported.

Hazard identification: determination of substances of concern, their adverse effects, target populations, and conditions of exposure, taking into account toxicity data and knowledge of effects on human health, other organisms, and their environment.

Hypersensitivity: state in which an individual reacts with allergic effects following exposure to a certain substance (allergen) after having been exposed previously to the same substance.

In silico: phrase applied to data generated and analyzed using computer modeling and information technology.

In vitro: in glass, referring to a study in the laboratory usually involving isolated organ, tissue, cell, or biochemical systems.

In vivo: In the living body, referring to a study performed on a living organism.

Lethal dose (LD): amount of a substance or physical agent (e.g., radiation) that causes death when taken into the body.

Lowest-effective dose (LED): lowest dose of a chemical inducing a specified effect in a specified fraction of exposed individuals.

Lowest published toxic dose (Toxic Dose Low, TDLo): the lowest dosage per unit of bodyweight (typically stated in milligrams per kilogram) of a substance known to have produced signs of toxicity in a particular animal species.

Lowest-observed-adverse-effect level (LOAEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure.

Lowest-observed-effect level (LOEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes any alteration in morphology, functional capacity, growth, development, or life span of target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Material safety data sheet (MSDS): compilation of information required under the U.S. OSHA Hazard Communication Standard on the identity of hazardous substances, health and physical hazards, exposure limits, and precautions.

Maximum permissible daily dose (MPDD): maximum daily dose of substance whosepenetration into a human body during a lifetime will not cause diseases or health hazards that can be detected by current investigation methods and will not adversely affect future generations.

Maximum tolerable dose (MTD): highest amount of a substance that, when introduced into the body, does not kill test animals (denoted by LD0).

Maximum tolerable exposure level (MTEL): maximum amount (dose) or concentration of a substance to which an organism can be exposed without leading to an adverse effect after prolonged exposure time. Maximum tolerated dose (MTD): high dose used in chronic toxicity testing that is expected on the basis of an adequate sub-chronic study to produce limited toxicity when

administered for the duration of the test period.

Median lethal dose (LD50): statistically derived median dose of a chemical or physical agent (radiation) expected to kill 50 % of organisms in a given population under a defined set of

conditions.

Mutagenicity: ability of a physical, chemical, or biological agent to induce (or generate) heritable changes (mutations) in the genotype in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof).

No-effect level (NEL): maximum dose (of a substance) that produces no detectable changes under defined conditions of exposure.

No-observed-adverse-effect level (NOAEL): greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

No-observed-effect level (NOEL): greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Quantitative structure–activity relationship (QSAR): quantitative structure–biological activity model derived using regression analysis and containing as parameters physicochemical constants, indicator variables, or theoretically calculated values.

Safety data sheet (SDS): single page giving toxicological and other safety advice, usually associated with a particular preparation, substance, or process.

Target (in biology): any organism, organ, tissue, cell or cell constituent that is subject to the action of an agent.